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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/626,219	07/26/2000	Jeffrey Browning	A046 US	7978

959 7590 08/24/2005

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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	09/626,219	BROWNING ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 11 April 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *21 March 2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☒ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): none.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: _____.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Misook Yu, 8/22/2005

Continuation of 11. does NOT place the application in condition for allowance because: Claims 20, 24-26, and 31-51, drawn to method of treating follicular lymphoma by administering composition comprising a soluble lymphotoxin beta receptor to a subject (base claims 20 and 43), to a mammal (claim 24) or to a human (claims 25), wherein the dependent claims 26, 36, 44, and 45 describe what happen after said administrating said composition, wherein dependent claims 31-33 further comprises another known cancer therapy, wherein claims 37-42, and 46-51 further limits what other things could be attached to said soluble lymphotoxin beta receptor. The new base claim 52 is drawn to method of treating follicular lymphoma in a human by administering a pharmaceutical composition comprising a polypeptide that comprises a soluble, ligand-binding domain of human lymphotoxin beta receptor to the subject, wherein the soluble, ligand-binding domain of human lymphotoxin beta receptor comprises SEQ ID NO:1.

Applicant argues that the examiner's reliance on Ponzio et al., the '351 patent would not convince one of skill in the art that the claimed invention require an undue experimentation because the instant specification demonstrate the efficacy of the soluble lymphotoxin beta receptor fused to human IgG Fc in treatment of SJL/RCS mice. Applicant argues that the Office's reliance on applicant's provided on 6/22/200, Appendix A, referred to as the "Gommerman review", Gommerman and Browning, Nature Reviews Immunology, 2003 J, 642, is inappropriate because the reference does not provide objective evidence that would cause one of to doubt the asserted utility of a soluble LtbetaR for treatment of the lymphoma.

These arguments have been fully considered but found unpersuasive because Gommerman reference discloses that the distinction exists between signaling of soluble LT alpha and that of the LT alpha/beta heterodimer complex. Reliance on references to infer the effect of treatment with the soluble LT beta receptor of the instant invention is inappropriate. The Gommerman review teaches the unique signaling role of surface LT through LT beta receptor. Furthermore, the Gommerman review discusses the impact of the in vivo microenvironment on surface LT-LT beta receptor complex signaling, stating that surface LT expressed on the surface of some B cells functions to maintain FDCs (follicular dendritic cells) in a fully functional state, the loss of surface LT-LT beta receptor complex signaling in the splenic marginal zone results in the loss of various marginal-zone myeloid populations and marginal- zone B cells. Neither of these roles for surface LT-LT beta receptor complex signaling supports the Examiner's conclusion that inhibition of the LT signaling system, as presently described in the art, would inherently lead to greater cell proliferation. Ponzio et al. teach the use of SJL mice to determine the effect of gamma-irradiation and cyclophosphamide administration on transplantation of spontaneous reticulum cell sarcomas (RCS). Administration of gamma- irradiation or cyclophosphamide to SJL mice was found to prevent transplantability of primary RCS, and to diminish the growth of established transplantable RCS lines. Thus, the conclusions of the Ponzio et al. reference are derived from studies of y- irradiated or cyclophosphnmide-treated SJL/RCS mice. In contrast, data presented in the instant specification describe treatment of SJL/RCS mice using soluble LT beta receptor and there is no reason for a skilled artisan to think that the administration of a soluble LT beta receptor (a much more targeted and subtle treatment than gamma- irradiation or cyclophosphamide) would have any inhibitory effect on transplantation per se. These arguments have been fully considered but found unpersuasive for following reasons.

The Office considered the data presented in the instant specification as well as what is known about the activity of a soluble lymphotoxin beta receptor in the art including applicant's numerous US patents and WIPO documents as well as other peer-reviewed journal articles. US Patent 5, 925, 351 (one inventor common with the instant application) at Figure 2 (note the Figure legend at column 4 lines 63-65) teaches that a soluble lymphotoxin beta receptor inhibits LT-induced cell death. The '351 patent teaches at the abstract that a soluble lymphotoxin beta receptor binds to its ligand, lymphotoxin, thereby blocking LT signaling.

As for the lower LN weight observed for SJL/RCS mice who received the soluble lymphotoxin beta receptor, one in the art might look for explanation elsewhere because Ponzio et al (IDS, 1986, Intern. Rev. Immunol., vol. 1, pages 273-301) at page 288-291 teach unlike other tumor growth, immunosuppression have an adverse effect to transplantability of RCS. US Patent 5, 925, 351 at Fig. 5 and in the claims teaches a soluble lymphotoxin beta receptor results in immunosuppression. The Gommerman review (note this review was published 3 years after the instant application had been filed) at page 651, left column teaches that lymph-node microenvironment is still frontier at the time the review paper is published. The Gommerman review teaches that the administration of LT beta receptor -immunoglobulin fusion protein decreases the cellularity in Peyer's patches and can reduce marked expansion of T- and B-cell numbers in a lymph node. Based on Ponzio et al., of record and the '351 patent of record, the Gommerman review, one would conclude that the lower LN weight SJL/RCS mice who received the soluble lymphotoxin beta receptor fusion protein might be due to the decreased cellularity in Peyer's patches and/or reduced T- and B-cell numbers in a lymph node. One skilled in the art would have questioned the efficacy of a soluble lymphotoxin beta receptor in treatment of lymphoma since the art as a whole teaches the cells in a lymph-node would decrease by administration of a soluble lymphotoxin beta receptor, leading to less weight of LN..

MISOOK YU
PATENT EXAMINER